

## Abstract

Influenza is an important respiratory pathogen that infects several million people each year. Currently available flu vaccines have to be updated regularly in order to be effective as the virus changes its composition by antigenic drift and shift. Most of the antibody response generated by these vaccines is strain specific as it is directed against the head domain (HA1) of HA.

The HA2 subunit of hemagglutinin is highly conserved and immunogens designed from this subunit are likely to provide protection against multiple strains of the virus. However, expression of HA2 alone in the absence of HA1 resulted in a protein that took up the low pH conformation of HA. Our goal was to design immunogens from HA2 that would fold into the neutral pH form.

Sequence analysis of a large number of HA protein sequences was carried out to identify conserved and exposed regions on HA. Several peptide and protein constructs were designed from the stem region of HA. These proteins were expressed in bacteria and purified proteins were used to immunize mice. Immunized mice were challenged with a lethal dose of virus to test for efficacy of the immunogen.

Using this approach, stem domain constructs of HA were successfully designed and shown to take up the neutral pH form. These immunogens were also shown to be capable of providing broad range protection. Residues involved in the low pH induced conformational change of HA were identified from studies on HA2 derived peptides.